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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,045	10/21/2003	De-Chao Yu	CELL-018CON	8701

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Piper Rudnick
1200 Nineteenth Street, N.W.
Washington, DC 20036-2412

EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,045	YU ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005 and 12 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-88* is/are pending in the application.

4a) Of the above claim(s) *88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/21/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 6/15/05 and 10/12/05. Claims 1-58 have been canceled. Claims 59, 61, 62, 67, 69, 74, 76-78 and 80-83 have been amended. Claims 59-88 are pending in this application. Claim 88 has been withdrawn from examination. Therefore, claims 59-87 are under examination in this application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Claim Objections

Claims 74 are objected to because of the following informalities: a word is missing between the word "mutation" and the word "a partial". Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 59- 62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 are rejected under 35 U.S.C. 102(a) as being anticipated by Chang et al (WO 99/25860; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and**

restated below. The rejection has been slightly reworded based upon applicants' arguments.

Chang et al teach an adenovirus vector that is selectively replicative and comprises gene for replication under control of a tissue specific promoter that further comprises transgenes. The transgene and the gene essential for replication can be linked by an IRES (see e.g. page 18, paragraph 2, page 29, paragraph 2 and figure 7). The gene essential for replication is any adenoviral gene that is essential for replication such as early or late genes (see e.g. page 15, paragraph 5). Specifically cited are E1A, E1B, E2, E3 or E4 (see e.g. bridging paragraph page 21-22). However, the specification teaches that the gene is essentially any gene that is required for the life cycle of the virus, which inherently includes late genes (see e.g. page 32, paragraph 2). Tissue specific promoters contemplated for use are mucin, CEA, PSA, tyrosinase or AFP (see e.g. page 29, paragraph 4). Cytotoxic genes include diphtheria toxin A, HSV-tk. Alternatively the transgene can be a cytokine such as GM-CSF or a reporter gene (see e.g. figure 1B, bridging paragraph 30-31 and page 29, paragraph 5). The first gene has a mutation in the transcriptional regulatory region, which comprises promoters and enhancers (see e.g. bridging paragraph page 17-18 and page 18, paragraph 2). It is inherent in the design of the construct that the second promoter be deleted of its endogenous promoter as the use of the IRES is for expression of the two genes by a singe regulatory sequence (see e.g. page 18, paragraph 2). This deletion constitutes a mutation in the promoter as recited in the claims. Cells and composition comprising the adenovirus are taught (see e.g. example 3). On page 16, Chang et al teach that the native transcriptional regulatory sequences may be rendered dysfunctional or may be disabled by partial removal (deletion) or other mutation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 59- 62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) in view of

This is a new rejection necessitated by applicants' amendment.

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element. The second gene has a mutation or a partial deletion of its endogenous promoter and is under translational control of an internal ribosome entry site (IRES). Furthermore

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach that the second gene has a partial deletion in its promoter.

Nanbru et al teach construction of a bicistronic vector for expression of a first and second coding sequence separated by a c-myc leader sequence (see e.g. figure 1). The leader sequence comprises the native promoters as well as leader sequences (see e.g. page 32061, col 1, paragraph 3). The native c-myc promoters are partially deleted in the bicistronic vector (see e.g. figure 1) to delete promoter P0, P1 and then P2. The goal is to initiate transcription from some

or all of these promoters but to allow for cap-independent initiation of translation of the second gene within the bicistronic vector .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tissue specific promoter taught by Chang et al with the kallikrein promoter or uroplakin II promoter or E2F promoter taught by Yu et al or Lin et al or Roelvink et al because Chang et al teach that it is within the ordinary skill of the art to generate a selectively replicating adenovirus by introducing a tissue specific promoter into the adenovirus and because Yu et al and Lin et al and Roelvink et al teach that it is within the ordinary skill of the art to use kallikrien, E2F and uroplakin promoters for tissue specific expression. One would have been motivated to do so in order to generate potential therapeutics in which adenovirus are selectively replicative in neoplasia (see e.g. Yu et al, page 1503, col 2). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 63, 64, 66 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) in view of Yu et al (Cancer Research, 1999; see entire document) or Lin et al (PNAS, 1995; see entire document) or Roelvink et al (US 2001/0047081; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and restated below.**

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of a TRE that is from human glandular kallikrein or uroplakin or E2F-1. Chang et al do not teach that the transgene is a reporter such as luciferase or β-glactosidase.

Yu et al teach identification of the transcriptional regulatory sequence of human kallikrein 2 (hK2) that is selectively inducible in prostrate to generate potential therapeutics in which adenovirus are selectively replicative in neoplasia (see e.g. Yu et al, page 1503, col 2). Yu et al generated a recombinant adenovirus comprising the hK2 promoter driving expression of luciferase to assay its activity and inducibility (see e.g. figure 1). Furthermore, to generate a selective replicating adenovirus, hK2 was used to express E1b in a vector also comprising E1A (see e.g. fig 4).

Lin et al teach identification of a promoter that is selectively expressive in the suprabasal urothelial cells (see e.g. abstract). The urothelial promoter sequences are linked to a reporter gene, β -galactosidase and its tissue specificity was assayed. The promoter was expressive only in bladder (see e.g. figure 4 and 5).

Roelvink et al teach that the E2F promoter provides targeted gene expression in prostate cancer cells (see e.g. paragraph 0023).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tissue specific promoter taught by Chang et al with the kallikrein

promoter or uroplakin II promoter or E2F promoter taught by Yu et al or Lin et al or Roelvink et al because Chang et al teach that it is within the ordinary skill of the art to generate a selectively replicating adenovirus by introducing a tissue specific promoter into the adenovirus and because Yu et al and Lin et al and Roelvink et al teach that it is within the ordinary skill of the art to use kallikrien, E2F and uroplakin promoters for tissue specific expression. One would have been motivated to do so in order to generate potential therapeutics in which adenovirus are selectively replicative in neoplasia (see e.g. Yu et al, page 1503, col 2). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 71 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) in view of Perez and White (Journal of Cell Biology, 1998; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and restated below.**

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of Fas as the cytotoxic gene in which E1B 19K is deleted.

Perez and White teach that Fas mediated apoptosis leads to cell killing triggered by Fas ligand. E1B 19K blocks Fas mediated apoptosis (see e.g. abstract). It would have been obvious

to delete E1B 19K in an adenovirus carrying FAS for the cytotoxic effects of Fas mediated apoptosis to occur.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cytotoxic transgene expressed by the adenovirus taught by Chang et al with a FAS gene in which the E1B 19K gene is deleted or mutated based upon the teachings of Perez and White because Chang et al teach that it is within the ordinary skill of the art to express a cytotoxic gene from adenovirus for cell killing and because Perez and White teach that Fas cell killing is blocked by E1B 19K. One would have been motivated to do so in order to receive the expected benefit of unhampered apoptotic cell killing in conditions taught by Chang et al in which cell killing is desired. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) in view of Stein et al (Molecular and Cellular Biology, 1998; see entire document) or Borman et al (NAR, 1995; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/15/05 and restated below.**

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of specific IRES sequence such as from EMCV or VEGF.

Stein et al teach isolation and utilization of the VEGF IRES that is effective in promoting cap-independent translation of mRNA (see e.g. abstract). Stein et al teach that the advantage of the VEGF IRES is the capacity for cap-independent translation in situations when overall protein synthesis is compromised (see e.g. page 3115, col 2). Internal ribosome entry is said to improve the competition with other mRNAs which otherwise would have rendered the translation of the mRNA an inefficient process (see e.g. page 3118, col 1).

Borman et al compare the activity of a variety of IRES sequences. EMCV is the most efficient at mediating expression (see e.g. figure 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the IRES taught by Chang et al with the VEGF IRES sequence such as described by Stein et al or the EMCV IRES as described by Borman et al because Chang et al teach that it is within the ordinary skill of the art to express a bicistronic and because Stein et al and Borman et al teach that it is within the ordinary skill of the art to use IRES for bicistronic expression. One would have been motivated to do so in order to receive the expected benefit of cap-independent translation in situations when overall protein synthesis is compromised or for highly efficient expression. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 102 and 103 on pages 10-14 of the amendment filed 6/15/05. Applicants argue that Chang et al do not anticipate the instant claims as they do not recite each and every element of the claims. Specifically, applicants argue that Chang et al do not mention constructs where the native transcriptional regulatory sequence of the second gene has a partial deletion or mutation. Furthermore, applicants argue that the secondary references do not cure the deficiency of Chang et al.

Applicants' arguments filed 6/15/05 have been fully considered but they are not persuasive. The claims as amended recite that the second gene has a mutation or a partial deletion of its endogenous promoter and is under translational control of an internal ribosome entry site (IRES). Chang et al teach construction of a vector in which a heterologous gene is linked to a gene essential for replication, a first gene, through an IRES sequences. It is inherent in the design of such a vector that the native promoter for the heterologous gene be modified such that expression of the heterologous gene is under control of the IRES sequence. Furthermore, Chang et al teach that the native promoter for the adenovirus gene is replaced with a heterologous transcriptional regulatory sequence. In this case, Chang et al teach that the "native transcriptional regulatory sequences may be disabled or rendered dysfunctional by partial removal (deletion) or other mutation (one or more base changes, insertions, inversions, etc.)." (page 16, paragraph 4). As both the adenoviral gene and the heterologous gene require that the native regulatory sequence be removed, Chang et al teach that this can be accomplished by partial removal of the native promoter. Any deletion , whether complete or partial constitutes a

mutation of the endogenous promoter of the heterologous gene and hence Chang et al do anticipate the instant claims.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1633

December 15, 2005

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER